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<b>(54) Title:</b> TOPICAL RADIOPROTECTIVE GEL FOR MUCOSA  <b>(57) Abstract</b>  The radioprotective gel comprises one or more vasoconstrictive substances, a pharmaceutically acceptable thickening agent, and water.		

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TOPICAL RADIOPROTECTIVE GEL FOR MUCOSAField of the invention

The present invention relates to a topical radio-protective gel for mucosa and comprises a vasoconstrictive substance, a pharmaceutically acceptable thickening agent, and water.

Background

Radiation therapy of tumours frequently causes secondary effects in the form of inflammation of the adjoining mucosa. Especially patients undergoing radiation therapy in the small pelvic region frequently acquire inflammation of the mucosa in the rectum and colon sigmoideum. Depending on the radiation dose and the length of the treatment, the inflammation may lead to fibrosis and obstruction of the bowel.

Since the beginning of the 1900's it has been known (G. Schwarz, Münch. med. Wochschr., 56, 1217 (1909)) that tissue hypoxia gives a radioprotective effect. Since then, different ways of inducing tissue hypoxia have been investigated, and these investigations were particularly concerned with the temporary mechanical blocking of mesenterial circulation by means of degradable starch microspheres, or with the selective inhibition of mucosal circulation by means of pharmacological drugs. Among the latter, epinephrine and lysine-vasopressin have so far been tested intra-arterially in animals (Steckel et al, Radiology 92, 1341 (1969), S. Borgström et al, British Journal of Radiology 55, 568-573 (1982) and S. Borgström et al, Acta Radiological Oncology 24 (1985), Fasc. 5) in order to protect either the kidneys or the mucosa of the small bowel. Furthermore, norepinephrine together with sodium sulphite has been tested locally in the rectum of rats by drop infusion (B. Larsson and S. Sténson, Nature, Vol. 205, pp. 364-365 (1965)) in

order to protect the rectal mucosa.

In the radiation treatment of tumours, the radiation treatment schedule varies, but up to 30 consecutive treatment days is not unusual, and radiation damage  
5 may show already after few days. Secondary effects from the bowel are often therapy-limiting in the radiation treatment of the small pelvic region.

The disadvantages encountered in the intra-arterial administration of vasoconstrictive substances  
10 in order to induce hypoxia in the mucosa are on the one hand systemic effects, such as blood pressure increase and bradycardia, and, on the other hand, that the patient must have the injection in direct connection with the radiation treatment since the  
15 time for the treatment proper is critical because of the short maximum hypoxic effect of certain drugs and because the radiation treatment possibly must take place before the drug has had time to affect the blood supply to the tumour. In addition, intra-  
20 arterial administration requires specially trained personnel, for which reason intra-arterial administration here will hardly become a routine technique.

There thus is need for a relatively long-term radioprotective drug against mucosa which is readily  
25 administered and which, furthermore, has no generic circulatoric effects.

#### Description of the invention

It has now surprisingly been found that vasoconstrictive substances can be administered topically  
30 to mucosa and provide the desired hypoxic effect if administered in gel form.

The present invention comprises a topical radioprotective gel for mucosa, which eliminates the disadvantages encountered in intra-arterial administration  
35 of vasoconstrictive substances.

The topical radioprotective gel according to the invention is the first topically applicable gel

for the radioprotection of mucosa.

The topical radioprotective gel according to the invention comprises one or more vasoconstrictive substances, a pharmaceutically acceptable thickening agent, and water. The vasoconstrictive substance must induce the desired hypoxic effect in the mucosa, and suitable substances are one or more substances selected among vasoconstrictive vasopressin derivatives, such as triglycyl-lysine-vasopressin, lysine-vasopressin, arginine-vasopressin, ornithine-vasopressin, phenylalanine-lysine-vasopressin, 2-Phe-3-Ile-8-Orn-vasopressin and 1-deamino-2-Phe-3-Ile-8-Orn-vasopressin, as well as Angiotensin II, norepinephrine and epinephrine.

The thickening agent should be inert, pharmaceutically acceptable and have adequate stability. The thickening agent should impart to the formulation appropriate rheological properties, such as

- keeping the active substance at the application site for an appropriate time, i.e. the apparent viscosity of the formulation at low stress should be higher than for water;
- a flexible formulation which is not irreversibly altered by the administration process, i.e. when exposed to higher stress.

Preferably, use is made of pharmaceutically acceptable thickeners possessing a shear thinning behaviour (i.e. imparting to the formulation an apparent viscosity which is a diminishing function of the applied stress). For instance, such formulations may be either pseudo-plastic or thixotropic in nature. Soluble polymers, such as carboxypolymethylene, derivatives of cellulose (e.g. carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose), natural gums (e.g. xanthan, guar) or derivatives of alginic acid (e.g. sodium alginate), will provide a formulation with shear thinning properties (pseudo-plastic). The use

of insoluble hydrocolloids, such as microcrystalline cellulose, will impart to the formulation a thixotropic behaviour. Also mixtures of the above-mentioned types of thickeners can be used to achieve appropriate rheological behaviour. The water used in the gel preferably is sterile deionised water.

Naturally, the radioprotective gel according to the invention may also include conventional pharmaceutical, inert additives, such as stabilisers, salts and preservatives according to the the US and European Pharmacopoeias.

By "gel" is meant, in the context of the present invention, a liquid which is more viscous than water to facilitate its retention on the mucosa during radiation treatment.

The topical radioprotective gel according to the invention may be applied e.g. rectally about 15 min. before radiation treatment of the small pelvic region. To be sure, the pharmacological effect need not be present for more than a few seconds, but the point of time of the radiation treatment is no longer critical because of the gel according to the invention yields the vasoconstrictive substance during a relatively long period of time.

The characteristic features of the radioprotective gel according to the invention will appear from the appended claims.

The vasoconstrictive substances preferred at present are Angiotensin II, norepinephrine and vasopressin derivatives having the following established structural formulae:

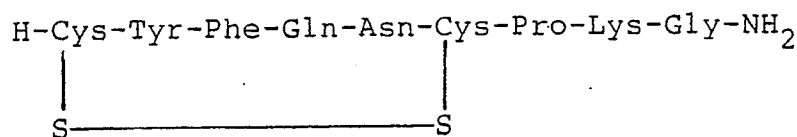
Triglycin-lysine-vasopressin (TGLVP)

H-Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH<sub>2</sub>



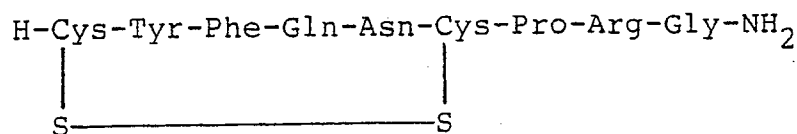
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Lysine-vasopressin (LVP)



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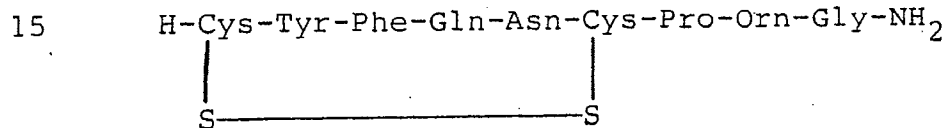
Arginine-vasopressin (AVP)



10

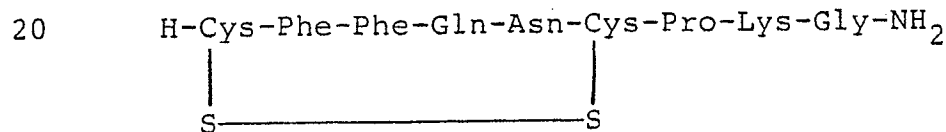
Other suitable vasoconstrictive vasopressin derivatives are:

Ornithine-vasopressin



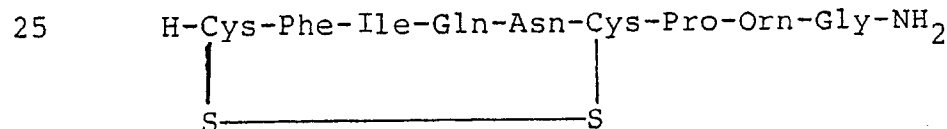
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Phenylalanine-lysine-vasopressin



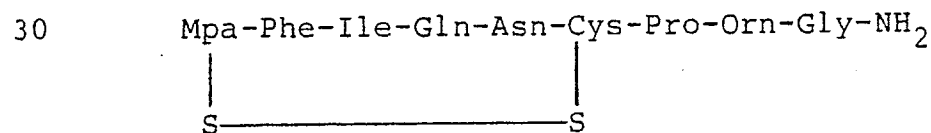
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2-Phe-3-Ile-8-Orn-vasopressin



25

1-deamino-2-Phe-3-Ile-8-Orn-vasopressin



30

(Mpa = Mercaptopropionyl)

35

The amounts of the various ingredients included in the topical radioprotective gel are not critical,

and the expert will have no difficulty in testing out suitable amounts that give the desired properties which are adequate hypoxic effect, stability and sterility as well as a suitable viscosity to facilitate  
5 maintaining the gel in contact with the mucosa during a suitable period of time. Naturally, the amount of the vasoconstrictive substance depends upon which substance is used in a specific case in order to give a suitable hypoxic effect, and this applies also to  
10 the thickening agent employed to provide an aqueous solution thereof having suitable viscosity properties and a suitable release of the vasoconstrictive substance or, where appropriate, a mixture of substances.

The concentration of vasoconstrictive substance  
15 in the radioprotective gels according to the invention was determined according to the desire to provide a local vasoconstrictive effect (with subsequent hypoxia) in the mucosa, but without general secondary effect, such as blood pressure increase and bradycardia. To  
20 achieve this, dose titration studies of the different vasoconstrictive substances were carried out, i.e. the dose just below the threshold of general circulatory response was defined. Due to interaction (electrostatic binding) between the active substance and the different  
25 thickening agents, the dose for a specific vasoconstrictive substance varied depending upon the thickening agent employed.

Examples of topical radioprotective gels that have been found to function as intended in radioprotective experiments, are 1600-6400 µg TGLVP per g of  
30 1% by weight carboxymethyl cellulose in sterile deionised water, 10 µg AVP per g of 0.2% by weight carboxypolymethylene in sterile deionised water, 32 µg LVP per g of 1.2% by weight hydroxyethyl cellulose  
35 in sterile deionised water, 250 µg Angiotensin II per g of 0.6% by weight hydroxyethyl cellulose in sterile deionised water, and 2 mg norepinephrine per g of



0.6% by weight hydroxyethyl cellulose in sterile de-ionised water.

To show the effect of radioprotective gels for the mucosa on topical application, a number of tests  
5 were carried out.

For studies of systematic circulation, Wistar rats (body weight 177-296 g) were used. TGLVP was administered rectally by means of a Nelaton-Foley catheter inserted through the anus until the balloon  
10 was 5 cm away from the anus. The balloon was then filled to ensure that the catheter stayed in position and to prevent TGLVP from reaching the upper parts of the bowel. TGLVP was dissolved in a 1% by weight aqueous solution of sodium carboxymethyl cellulose  
15 (CMC) and was in contact with all parts of the mucosa during the test. The volume applied amounted to half a milliliter. Three dose levels of TGLVP were tested, i.e. 800 µg, 1600 µg and 3200 µg. For each dose level, use was made of five rats and a corresponding number  
20 of controls which were given CMC solution only. For anaesthesia, nembutal was used intraperitoneally. Mean values for arterial pressure and puls rate were recorded by means of a catheter in the aorta via the femoral artery.

25 The results of these tests show that the doses 800 µg and 1600 µg gave no systemic circulatory response in the form of blood pressure increase or lower pulse. 3200 µg, on the other hand, caused blood pressure increase in several animals.

30 Dose titration was carried out in a similar manner on AVP, LVP, TGLVP with other thickening agents, Angiotensin II and norepinephrine.

The following results were obtained.

35 25 µg and 50 µg AVP were given in 0.2% by weight carboxypolymethylene solution without any significant influence on blood pressure (pulse rate was not mea-

methylene solution in a dose of 10  $\mu\text{g}$  and 20  $\mu\text{g}$  without any significant change in blood pressure (pulse rate was not measured). The dose of 40  $\mu\text{g}$  and 80  $\mu\text{g}$  gave a rise in blood pressure (40  $\mu\text{g}$  significant at 10, 15, 20, 25, 45 and 60 minutes after application, 80  $\mu\text{g}$  significant 5-60 minutes after application).

LVP in 1% by weight sodiumcarboxymethyl cellulose (CMC) solution was given in a dose of 10  $\mu\text{g}$ , 20  $\mu\text{g}$  and 40  $\mu\text{g}$  without any change in blood pressure (pulse rate was not measured). 80  $\mu\text{g}$  LVP caused a rise in blood pressure 5-45 minutes after application.

LVP in 1.2% by weight hydroxyethyl cellulose solution was given in a dose of 4  $\mu\text{g}$ , 8  $\mu\text{g}$  and 16  $\mu\text{g}$  without significant changes in systemic circulation. 32  $\mu\text{g}$  caused a rise in blood pressure 5, 10, 15, 20, 25, 30, 45, 75 and 90 minutes after application. No decrease in pulse rate was noted.

TGLVP in 0.9% by weight hydroxypropyl cellulose solution was given in doses of 128  $\mu\text{g}$  and 256  $\mu\text{g}$  without changes. 512  $\mu\text{g}$  gave a bradycardia 15-120 minutes after application. With said solution there was a notable tendency to rise in blood pressure in the control group.

TGLVP was also given in 1.2% by weight hydroxyethyl cellulose solution. The dose of 128  $\mu\text{g}$  gave no circulatory changes. 256  $\mu\text{g}$  gave a rise in blood pressure at 75 and 90 minutes after application. There was also a decrease in pulse rate at 5 minutes after application. 512  $\mu\text{g}$  gave a rise in blood pressure 30 and 45 minutes after application and a bradycardia 10-45 minutes after.

Dose titrations with doses of 0.1  $\mu\text{g}$  to 500  $\mu\text{g}$  Angiotensin II in 0.6% by weight hydroxyethyl cellulose solution were administered to rats, but no significant changes in blood pressure or pulse rate were observed even at the highest dose level during 75 or 140 minutes of follow-up time.

Dose titrations with doses of 150 µg, 500 µg, 750 µg, 1000 µg and 2000 µg norepinephrine in 0.6% by weight hydroxyethyl cellulose solution were administered to rats. No significant changes in blood pressure or pulse rate were observed at doses of up to 750 µg, but a slight increase in blood pressure was observed at the doses 1000 µg and 2000 µg.

For studies of the radioprotective effect of TGLVP Wistar rats (body weight 187-394 g) were used and treated in pairs at the same time. In each pair, one rat was treated rectally with TGLVP, while the other rat, the control rat, was given CMC solution rectally. The gels were applied in the same manner as described above. For anaesthesia, nembutal was given intraperitoneally. The rats were irradiated with 240 kV X-rays (0.2 Cu filtration), using AP and PA fields in size 4 x 3 cm. This gave a uniform dose in the lower part of the abdomen corresponding to the position of the rectum. 10 Gy were given on day 1, and 10 Gy on day 4. The rats were killed 14 days after the treatment, and the rectum was removed for histological analysis. The rats were weighed before treatment and when they were killed.

10 rats were treated with 1600 µg TGLVP 15 min before irradiation (Tables IV and V)

5 rats were treated with 800 µg TGLVP 15 min before irradiation (Table V)

10 rats were given 1600 µg TGLVP 30 min before treatment (Table III)

5 rats were given 3200 µg TGLVP 15 min before treatment (Table I)

5 rats were given 3200 µg TGLVP 30 min before

Histological grading (sum of parameters) was performed in accordance with an evaluation system in which 0 is the normal structure and 6 indicates maximum change. Irradiation-induced lesions in the mucosa were determined arbitrarily by means of the following parameters:

- 1: The extent of fibrosis in the mucosa and submucosa.
- 2: The change of glandular structure in the mucosa.
- 10 3: Ulcerations in the mucosa or abscesses in mucosal crypts.

The results obtained are shown in Tables I-V. Table VI shows a corresponding radioprotective test with AVP, in which only histological grading was performed.

Table VII concerns a corresponding radioprotection test with LVP.

Table VIII concerns a corresponding radioprotection test with Angiotensin II.

Table IX concerns a corresponding radioprotection test with norepinephrine.

TABLE 1

15 min

IGLVP 6400 µg/g 1 weight% carboxymethyl cellulose in water

at No.	1	2	3	4	5	6	7	8	9	10
ose (µg)	-	3200	-	3200	-	3200	-	3200	-	3200
ibrosis	4	2	4	2	4	2	6	2	4	4
hange of glandular tructure	6	2	6	0	6	0	6	2	6	4
lceration - abscessa evelopment in crypts	4	2	4	0	4	0	4	0	6	4
um of parameters	14	6	14	2	14	2	16	4	16	12
ody weight change (g)	5	4	14	7	5	15	0	12	4	9

TABLE II

30 min

IGLVP 6400 µg/g 1 weight% carboxymethyl cellulose in water

Rat No.	11	12	13	14	15	16	17	18	19	20
Dose (µg)	-	3200	-	3200	-	3200	-	3200	-	3200
Fibrosis	6	4	6	4	6	4	6	4	6	4
Change of glandular structure	6	4	6	0	4	2	6	2	6	0
Ulceration - abscessa development in crypts	6	4	6	2	4	0	4	2	6	0
Sum of parameters	18	12	18	6	14	6	16	8	18	4
Body weight change (g)	24	7	46	13	0	-2	9	38	22	24

TABLE III

30 min

IGLVP 3200 µg/g 1 weight% carboxymethyl cellulose in water

Rat No.	21	22	23	24	25	26	27	28	29	30
Dose (µg)	-	1600	-	1600	-	1600	-	1600	-	1600
Fibrosis	6	4	4	2	6	4	6	4	6	4
Change of glandular structure	6	2	4	2	6	2	6	4	6	2
Ulceration - abscessa development in crypts	6	0	2	2	6	0	6	2	4	0
Sum of parameters	18	6	10	6	18	6	18	10	16	6
body weight change (g)	-2	3	9	18	-4	7	-7	5	0	14

TABLE III (cont'd)

Rat No.	31	32	33	34	35	36	37	38	39	40
Dose ( $\mu$ g)	-	1600	-	1600	-	1600	-	1600	-	1600
Fibrosis	6	4	4	2	4	2	4	4	6	2
Change of glandular structure	6	2	6	2	4	2	6	2	6	2
Ulceration - abscessa development in crypts	6	0	6	2	6	2	4	4	6	0
Sum of parameters	18	6	16	6	14	6	14	10	18	4
Body weight change (g)	11	1	38	66	61	80	39	47	7	55



15

TABLE IV

15 minIGLVP in 1 weight% carboxymethyl cellulose in water

Rat No.	41	42	43	44	45	46	47	48	49	50
Dose (µg)	-	1600	-	1600	-	1600	-	1600	-	1600
Fibrosis	6	2	6	4	4	2	4	2	6	2
Change of glandular structure	6	2	4	2	4	2	4	2	4	2
Ulceration - abscessa development in crypts	4	2	4	0	4	0	4	0	4	0
Sum of parameters	16	6	14	6	12	4	12	4	14	4
Body weight change (g)	5	11	-7	20	1	3	4	3	7	3

TABLE V

15 minTGLVP in 1 weight% carboxymethyl cellulose in water

Rat No.	51	52	53	54	55	56	57	58	59
Dose (µg)	-	800	1600	-	800	1600	-	800	1600
Fibrosis	5	2	1	2	2	2	4	3	3
Change of glandular structure	5	1	0	3	1	0	4	2	2
Ulceration - abscessa development in crypts	5	1	0	2	0	0	4	2	1
Sum of parameters	15	4	1	7	3	2	12	7	6
Body weight change (g)	-5	-7	15	2	3	20	?	-14	11

TABLE V (cont'd)

Rat No.	60	61	62	63	64	65
Dose ( $\mu$ g)	-	800	1600	-	800	1600
Fibrosis	2	1	2	4	2	3
Change of glandular structure	2	1	1	3	2	1
Ulceration - abscessa development in crypts	2	1	0	3	3	1
Sum of parameters	8	3	3	10	7	5
body weight change (g)	?	-3	9	1	?	14

TABLE VI

10 min20 µg AVP, 0.2 weight% carboxymethylene in water, 1 ml

Rat No.	66	67	68	69	70	71	72	73
AVP (10 µg)	no	yes	no	yes	no	yes	no	yes
Histological grading	5	2	4	5	4	2	4	1

TABLE VII

15 min

LVP 32 µg/q 1.2 weight% hydroxyethyl cellulose in water

Rat No.	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89
Dose (µg)	-	16	-	16	-	16	-	16	-	16	-	16	-	16	-	16
Fibrosis	6	2	4	4	6	4	4	4	6	6	6	4	6	2	6	4
Change of glandular structure	4	0	4	2	6	6	6	4	6	6	6	4	6	2	6	2
Ulceration - abscessa development in crypts	4	0	4	4	6	6	6	4	4	6	6	4	4	0	6	2
Sum of parameters	14	2	12	10	18	16	16	12	16	18	18	12	16	4	18	8

TABLE VIII

15 minANGIOTENSIN II 250 µg/q 0.6 weight% hydroxyethyl cellulose in water

Rat No.	90	91	92	93	94	95	96	97	98	99	100	101
Dose µg	-	125	-	125	-	125	-	125	-	125	-	125
Fibrosis	6	4	4	4	4	4	6	4	6	4	6	6
Change of granular structure	6	4	4	6	6	4	6	4	6	4	6	6
Ulceration - abscessa development in crypts	4	6	4	4	6	6	6	6	6	4	6	4
Sum of parameters	16	14	12	14	16	14	18	14	18	12	18	16

TABLE IX

15 min

Norepinephrine 2 mg/g 0.6 weight% hydroxyethyl cellulose + 2 weight% ascorbic acid in water

Rat No.	102	103	104	105	106	107	108	109	110	111	112	113
Dose (mg)	-	1	-	1	-	1	-	1	-	1	-	1
Fibrosis	6	4	6	4	4	4	6	2	6	4	6	4
Change of granular structure	6	4	6	4	4	4	6	2	4	4	6	4
Ulceration - abscessa development in crypts	6	4	4	4	0	6	6	0	6	2	6	4
Sum of parameters	18	12	16	12	8	14	18	4	16	10	18	12

Tables I-V above, show that a dose of 3200, 1600 or 800  $\mu\text{g}$  TGLVP upon irradiation for 15 or 30 min after administration gave radioprotection to the mucosa as compared with the controls. Moreover, it appears  
5 from Tables I-IV that an increase of the dose from 1600  $\mu\text{g}$  to 3200  $\mu\text{g}$ , or an increase of the time from 15 to 30 min, does not seem to give a better result than 1600  $\mu\text{g}$  at 15 min.

10 Increasing the dose from 800  $\mu\text{g}$  to 1600  $\mu\text{g}$  gave an improved protection, as will appear from the body weight values shown in Table V.

A dose of 1600  $\mu\text{g}$  TGLVP thus gives maximum radioprotective effect to rats without general circulatory responses.

15 Table VI indicates that a dose of 10  $\mu\text{g}$  AVP upon irradiation 10 min after administration gave radioprotection to the mucosa, as compared with the controls.

20 Table VII indicates that a dose of 16  $\mu\text{g}$  LVP upon irradiation 15 min after administration gave radioprotection to the mucosa and caused no significant change in systemic circulation.

25 Table VIII indicates that a dose of 125  $\mu\text{g}$  Angiotensin II upon irradiation 15 min after administration gave, in 5 out of 6 cases, radioprotection to the mucosa, as compared with the controls.

Table IX indicates that a dose of 1 mg norepinephrine upon irradiation 15 min after administration gave, in 5 out of 6 cases, radioprotection to the mucosa, as compared with the controls.



## CLAIMS

1. A topical radioprotective gel for the mucosa, characterised in that it comprises one or more vasoconstrictive substances, a pharmaceutically acceptable thickening agent, and water.

5        2. A topical radioprotective gel as claimed in claim 1, characterised in that the vasoconstrictive substance is selected among triglycyl-lysine-vasopressin, lysine-vasopressin, arginine-vasopressin, ornithine-vasopressin, phenylalanine-  
10 -lysine-vasopressin, 2-Phe-3-Ile-8-Orn-vasopressin, 1-deamino-2-Phe-3-Ile-8-Orn-vasopressin, Angiotensin II, norepinephrine, and mixtures thereof.

3. A topical radioprotective gel as claimed in claim 2, characterised in that the vasoconstrictive substance is selected among triglycyl-  
15 -lysine-vasopressin, lysine-vasopressin, arginine-vasopressin, Angiotensin II, and norepinephrine.

4. A topical radioprotective gel as claimed in any one of claims 1-3, characterised in  
20 that the pharmaceutically acceptable thickening agent is selected among soluble polymers, such as carboxypolymethylene, cellulose derivatives, natural gums and alginic acid derivatives and/or insoluble hydrocolloids, such as microcrystalline cellulose.

25        5. A topical radioprotective gel as claimed in claim 4, characterised in that the pharmaceutically acceptable thickening agent is selected among carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and carboxypolymethylene.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/SE87/00359

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC <span style="float: right;">4</span>		
A 61 K 7/40, 9/06		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC 4 US C1	A 61 K 7/40, 9/00, /06, /08 424: 14, 59	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
SE, NO, DK, FI classes as above Medline Database		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	Chemical Abstracts, Vol 84, 1976 84: 12832v, Radiology 1975, 117(1), 199-203 (Eng)	
A	Chemical Abstracts, Vol 78, 1973, 24140g, Radiology 1972, 105(2), 425-8 (Eng)	
A	Chemical Abstracts, Vol 82, 1975, 81061p, Cancer (Philadelphia) 1974, 34(4), 1046-58 (Eng)	
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1987-10-19	1987 -10- 2 0	
International Searching Authority	Signature of Authorized Officer	